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Use of Medications for Treating Anxiety or Depression among Testicular Cancer Survivors: A Multi-Institutional Study

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Abstract

Background: This study examined sociodemographic factors, cisplatin-related adverse health outcomes (AHOs), and cumulative burden of morbidity (CBM_{Pt}) scores associated with medication use for anxiety and/or depression in testicular cancer survivors (TCS).

Methods: A total of 1,802 TCS who completed cisplatin-based chemotherapy ≥12 months previously completed questionnaires regarding sociodemographic features and cisplatin-related AHOs (hearing impairment, tinnitus, peripheral sensory neuropathy (PSN), kidney disease). A CBM_{Pt} score encompassed the number and severity of cisplatin-related AHOs. Multivariable logistic regression models assessed the relationship of individual AHOs and CBM_{Pt} with medication use for anxiety and/or depression.

Results: A total of 151 TCS (8.4%) used medications for anxiety and/or depression. No cisplatin-related AHO were reported by 511 (28.4%) participants, whereas 622 (34.5%), 334 (18.5%), 287 (15.9%), and 48 (2.7%), respectively had very low, low, medium, and high CBM_{Pt} scores. In the multivariable model, higher CBM_{Pt} scores were significantly associated with

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medication use for anxiety and/or depression ($P<0.0001$). Additionally, tinnitus ($P=0.0009$), PSN ($P=0.02$), and having health insurance ($P=0.05$) were significantly associated with greater use of these medications; whereas being employed ($P=0.0005$) and vigorous physical activity ($P=0.01$) were significantly associated with diminished use.

Conclusions: TCS with higher CBM_{Pt} scores had a higher probability of using medications for anxiety and/or depression and conversely, those who were employed and physically active tended to have reduced use of these medications.

Impact: Healthcare providers should encourage TCS to increase physical activity to improve both physical and mental health. Rehabilitation programs should assess work-related skills and provide career development counseling/training.

Introduction

Testicular cancer, the most common cancer affecting young men (18–39 years), is highly curable with a 10-year survival rate of 95% (1). The introduction of cisplatin-based chemotherapy (CBCT) in the 1970s largely contributed to this increased survival (1). However, the high cure rate is offset by long-term morbidities such as hearing loss (HL), tinnitus, peripheral neuropathy, and nephrotoxicity as well as psychosocial effects (anxiety, depression), cognitive impairment, and poorer health-related quality of life (2).

Testicular cancer survivors (TCS) can experience anxiety or depression due to cancer diagnosis or treatment, with prevalence estimates ranging from 10–20%, which when compared to normative populations are modestly greater for anxiety, but inconclusive regarding depression (3). Numerous socio-behavioral and psychological factors contribute to anxiety or depression. For example, anxiety is associated with younger age (4), lower educational levels (5–7), unemployment (5), living alone (7), economic concerns (4), alcohol abuse (4), sexual dysfunction (4), fear of relapse (4), prior psychological distress (4,7), and peripheral neuropathy (4). Depression in TCS is related to older age (7–9), lower educational level (6,7), living alone (7,10), previous psychological distress (7), low physical activity (11), and smoking (12).

A higher number of coexisting conditions also constitute risk factors for anxiety and/or depression in cancer survivors (13). The most prevalent adverse health outcomes (AHOs) related to CBCT in TCS are tinnitus, hearing impairment, and peripheral neuropathy (14,15). Our previous study showed that 16.4% TCS experience peripheral neuropathy plus tinnitus and/or hearing impairment (14). Both hearing impairment (16,17) and tinnitus (18) are associated with anxiety and depression in the general population, and peripheral neuropathy (4,19) is related to both conditions in cancer survivors. However, to our knowledge, no large study to date has investigated the association between the number and severity of cisplatin-related AHOs and anxiety and depression in TCS.

To provide new information with regard to the association of sociodemographic and cisplatin-related AHOs (hearing impairment, tinnitus, peripheral sensory neuropathy, kidney disease) (1,2,20) with the use of medications to treat anxiety and depression, we studied 1,802 TCS enrolled in the Platinum (Pt) Study, a large, multi-center clinical investigation.

We also evaluated the association between the cumulative burden of morbidity (CBM_{Pt}) score for cisplatin-related AHOs (1,2,20) and the use of these medications.

Methods

Study Population

Patients were enrolled in the Platinum Study at nine sites in the U.S., Canada, and United Kingdom. Cohort methods were described previously (14,15). Briefly, eligible patients had histological/serological diagnosis of germ cell tumor (GCT), were ≥18 years at consent, completed first-line CBCT for either initial GCT or recurrence after active surveillance, had no subsequent salvage chemotherapy, no radiotherapy, no antecedent chemotherapy for another primary cancer, and were followed-up routinely at enrolling sites. All participants were disease-free at clinical evaluation and referred to as TCS. Each enrolling site's institutional review board approved the investigation, and all participants provided written informed consent. This study included 1,802 TCS ≥12 months post-CBCT not treated with carboplatin.

Clinical, Sociodemographic, and Health Behavior Characteristics

Detailed clinical characteristics were abstracted from medical records by trained personnel. Collected data included cancer diagnosis and histology as well as treatment information (dates of administration, number of cycles, and cumulative cisplatin dose) as described previously (15).

Sociodemographic and health behavior information were collected through self-reporting at study enrollment using validated questionnaires (21–24). Sociodemographic characteristics included education, marital status, employment status, and health insurance coverage. Health behaviors included smoking status (never, former, current), alcohol consumption and physical activity in the past year. Participants were asked about types of physical activity and average time per week spent on each one. A metabolic equivalent task (MET) score was assigned to each physical activity based on its energy cost. One MET is defined as the amount of energy expended while sitting quietly (24). Vigorous physical activity was defined based on activities with MET value ≥6 (23).

Adverse Health Outcomes (AHO) and Cumulative Burden of Morbidity

AHOs including patient-reported HL, tinnitus, peripheral sensory neuropathy, and kidney disease were collected through validated questionnaires (25–27). AHOs were mapped to individual AHOs using a modified version of the CTCAE version 4.03 (28) and graded 0-to-4 based on severity (Supplementary Table S1) (15)

HL, tinnitus, peripheral sensory neuropathy, and kidney disease were included in a cisplatin-related cumulative burden of morbidity (CBM_{Pt}) score since each has been previously shown to be related to CBCT (1,2,20). A CBM_{Pt} score was calculated for each TCS based on the number and severity of AHOs following methods adapted from Geenen et al. (29) using a modified version described by Kerns et al (30) that removed autonomic neuropathy (Supplementary Table S1 and S2).

Use of Medications for Anxiety and Depression

Patient-reported prescription drug use included current medications at study enrollment if taken consistently for >1 month. TCS were also asked to provide the indication for each medication. Medications were categorized as used for anxiety and/or depression according to pharmacological classes defined by the National Center for Health Statistics (NCHS) (31,32), and included benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, phenylpiperazine antidepressants, tetracyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and miscellaneous antidepressants or anxiolytics (e.g., buspirone). Anxiety and/or depressive disorders were defined as anxiety, depression, obsessive compulsive disorder, panic attacks, and post-traumatic stress disorder. If patients reported that they used one of the listed medications for a disorder other than the ones specified, they were not considered users of medications for anxiety and/or depression.

Statistical Analysis

Percentages were used for categorical variables and medians (ranges) for discrete and continuous variables. Binomial logistic regression models tested the univariate association of sociodemographic characteristics, health behaviors, individual AHOs, and CBM_{Pt} with medication use for anxiety and/or depression (yes/no) as the dependent variable. Variables with Wald chi-square test $P \leq 0.25$ were included in the multivariable model following methods of Hosmer et al. (33). Two multivariable models were fitted: 1) variables selected from univariate models in addition to individual AHOs; 2) variables selected from univariate models in addition to CBM_{Pt}. Final multivariable models were developed by backward elimination of variables with Wald chi-square test $P > 0.10$. Odds ratios (OR) and 95% confidence intervals (CI) were reported for both univariate and multivariable (adjusted) models.

Multicollinearity between independent variables was assessed for final multivariable models using the variance inflation factor (VIF) (34). All tests were two-sided, with statistical significance $P < 0.05$. All analyses were performed using SAS version 9.4 (SAS Institute).

Comparison Population

The use of medications for anxiety and/or depression in our population was compared to that reported to the National Health and Nutrition Examination Survey (NHANES) for survey years 2017–2018 (35). NHANES is a program of the NCHS designed to obtain demographic, health, dietary, and laboratory data from a representative sample of U.S. residents. Utilization of medications for anxiety and/or depression was determined from self-reported medication use and self-reported medication indication. NCHS has classified medications to pharmacological classes including anxiolytics and antidepressants (31,32). Medication indication was classified using up to three International Classification of Disease-10 codes (F32.9: major depressive disorder, single episode, unspecified; F33.9: major depressive disorder, recurrent, unspecified; F41.0: panic disorder [episodic paroxysmal anxiety] without agoraphobia; F41.9: anxiety disorder, unspecified; F42: obsessive-compulsive disorder; F43.1: post-traumatic stress disorder (PTSD); and F43.9: reaction to severe stress, unspecified). Those who reported pain or other reasons as the

indication (M79.2: neuralgia and neuritis, unspecified; R53: malaise and fatigue; M79.7: fibromyalgia; M62.83: muscle spasm; M54: dorsalgia; M19.9: osteoarthritis, unspecified site; M79.1: myalgia; R52: pain, unspecified) for anxiety and/or depression medication use (N=9) were excluded.

To account for the complex sample design, the entire NHANEs population was used to estimate the standard errors, with subpopulation analysis to compare those who were male, ≥18 and ≤65 years, and without a history of cancer between the Platinum Study population and NHANES. For comparisons, published NHANES sampling weights, primary sampling units, and strata were used, while a strata, a primary sampling unit, and a weight of 1 was applied to our population. The logistic regression model for anxiety and/or depression medication use was adjusted for age, education, and race/ethnicity. Marginal standardization (36) was used to estimate predicted probabilities for anxiety and/or depression medication use in the Platinum Study and in NHANES, reflecting weighted averages over the confounder distributions of age, education, and race/ethnicity in NHANES. Estimates were performed in Stata v16.1.

Results

Population Characteristics

A total of 1,802 TCS were studied (Table 1). Median age at clinical evaluation and median time since chemotherapy completion were 37 years and 3.8 years, respectively. Over 90% of TCS were treated with etoposide and cisplatin with/without bleomycin (BEP/EP). Most participants were white (87.7%), college-educated (64.2%), employed (89%), and had health insurance (91%). Participants were largely never-smokers (57.3%) and had high engagement in vigorous physical activity (67.9%).

A total of 151 participants (8.4%) used medications for anxiety and/or depression in the Platinum Study. After adjustment for race/ethnicity, age, and education level to the NHANES distribution, the predicted probability for anxiety and/or depression medication use was 6.3% (95% CI: 4.61, 7.96) in the Platinum Study compared to 7.4% (95% CI: 5.20, 9.59%) in NHANES (*P*-value for difference =0.51). The odds ratio for anxiety and/or depression medication use in the Platinum Study was not significantly different than NHANES (OR=0.83; 95% CI: 0.47, 1.48).

Table 2 shows frequencies of CBM_{Pt} scores and individual AHOs among all TCS and stratified by medication use for anxiety or depression. Overall, only 511 (28.4%) participants reported no cisplatin-related AHO. CBM_{Pt} scores of very low, low, medium, and high were noted in 622 (34.5%), 334 (18.5%), 287 (15.9%), and 48 (2.7%) TCS, respectively. Among 1,651 TCS not taking medications for anxiety and/or depression, any grade of HL, tinnitus, peripheral sensory neuropathy, and kidney disease were reported by 36.3%, 37.8%, 53.7%, and 2.1% TCS, respectively. In contrast, corresponding percentages were greater (56.3%, 57.7%, 72.8%, and 4.7%, respectively) for 151 TCS using these medications. Similarly, the prevalence of higher scores for CBM_{Pt} (low, medium, and high) was greater in survivors using medications for anxiety and/or depression vs. those who did not take these medications.

Association of Sociodemographic, Health Behaviors, and AHOs with Medication Use for Anxiety and/or Depression

Supplementary Table S3 shows univariate associations of various factors and medication use for anxiety and/or depression. However, we emphasize here the multivariable results. In the final multivariable model (including tinnitus, peripheral sensory neuropathy, employment status, health insurance coverage, and engagement in vigorous physical activity), being employed (OR=0.39, 95%CI, 0.23–0.66) and engaging in vigorous physical activity (OR=0.63, 95%CI,0.44–0.89) were associated with significantly less use of medications for anxiety and/or depression, while having health insurance was associated with greater medication use (OR=2.15, 95%CI, 1.01–4.56) (Table 3). The likelihood of medication use for anxiety and/or depression was significantly increased among TCS with grade 2 tinnitus (OR=2.2, 95%CI, 1.25–3.88), grade 3 tinnitus (OR=2.74, 95%CI, 1.89–4.75), and grade 2 peripheral sensory neuropathy (OR=2.2, 95%CI, 1.33–3.63), with results for grade 3 neuropathy of borderline significance (OR=1.68; 95%CI, 0.99–2.87).

The second multivariable model (including CBM_{Pt} score, employment status, health insurance coverage, and engagement in vigorous physical activity) indicated similar results. Being employed (OR=0.38, $P<0.05$) and engaging in vigorous physical activity (OR=0.63, $P<0.05$) were associated with a significantly reduced use of medications for anxiety and/or depression, while having health insurance was associated with greater use (OR=2.12, $P<0.05$). Significantly increased odds for medication use for anxiety and/or depression were also observed among TCS with CBM_{Pt} scores of low (OR=2.96, 95%CI, 1.67–5.24), medium (OR=3.47, 95%CI, 1.95–6.18), and high (OR=3.18, 95%CI, 1.22–8.3) (Table 3). In addition, we also included country of enrollment in both multivariable models and found that study region (USA, UK, Canada) did not alter the association between employment status and use of medications for anxiety and depression. No multicollinearity was detected between variables in either model (VIF<5).

Discussion

In a large cohort of TCS (N=1,802), we investigated for the first time, four cisplatin-related AHOs (HL, tinnitus, peripheral sensory neuropathy, kidney disease) as well as CBM_{Pt} scores and sociodemographic characteristics in relation to the use of medications for anxiety and/or depression. New findings include that higher grades of tinnitus, peripheral sensory neuropathy, and a higher CBM_{Pt} score were significantly associated with increased use of these medications as was having health insurance. Conversely, being employed and engaging in vigorous physical activity were associated with a significantly lower use of these medications.

Anxiety and depression are associated with a reduced health-related quality of life (HRQOL) in TCS (37). Pharmacological or non-pharmacological interventions (cognitive behavioral therapy, stress reduction therapy, etc.) can be utilized for treatment (13), with evidence showing that antidepressant and anxiolytic medications are safe and effective in cancer patients (38–40). They are typically recommended for use in severe cases of anxiety and depression (41,42), but most cancer survivors do not discuss cancer-related psychological effects with healthcare providers (43) due to lack of awareness or

identification of symptoms as stigma (43,44). Only Hawkins et al.(45) investigated the characteristics of U.S. cancer survivors (80% aged ≥50 years) at higher risk of prescription use for anxiety and depression. Patients with various cancer types (e.g., breast, prostate, melanoma, cervix, colorectal, hematologic, ovary, uterus, and others) were studied, but it was not clear whether TCS were included. Hawkins et al.(45) analyzed only the number of comorbidities, not the related severity, associated with anxiolytic and antidepressant use. These investigators concluded that, in general, U.S. cancer survivors took medications for anxiety and depression about twice as frequently as the general population, likely due to cancer treatment-related physical and emotional distress (45). However, little is known with regard to the characteristics of U.S. TCS (46% age <50 years(46)) prescribed medications for anxiety and depression. To our knowledge, this large study is the first to identify characteristics of TCS associated with prescription medication use for anxiety and/or depression in addition to assessing the association with the number and severity of cisplatin-relation AHOs.

Factors Associated with Significant Use of Medications for Anxiety and/or Depression

CBM_{Pt} score.—To our knowledge, this is the first study to report an association between a greater CBM_{Pt} score and an increased use of medications for anxiety and/or depression in adult-onset cancer survivors. Our findings mirror those of Hawkins et al.,(45) who showed an increased use of these medications in cancer survivors with larger numbers of chronic health conditions. Previous investigations of risk factors for anxiety and depression among adult-onset cancer survivors also confirm associations of number of comorbid conditions with anxiety/depression (47,48). A higher number of comorbidities can result in greater complexities in disease management, the use of multiple prescription medications, less physical activity, and less social interaction (48). SEER-Medicare linkage studies of colorectal cancer survivors show a significant relationship between a higher number of comorbidities and poorer HRQOL, physical health, and anxiety and depression (48).

Tinnitus.—Higher grades of tinnitus were associated with a 2- to 3-fold greater use of medications for anxiety and depression. Although Dahl et al.(4) found no significant association between anxiety disorders in TCS and a combined variable of “tinnitus/hearing problems,” tinnitus was not evaluated independently. Moreover, Dahl et al. used a four-item likert scale, with responses analyzed as binary variables, e.g., by collapsing responses of “quite a bit” and “very much” as cases and responses of ‘none’ and ‘a little bit’ as controls. In contrast, we used a considerably finer grading of AHOs based on CTCAE criteria (15,28). In the general population, the association between tinnitus and anxiety and depression is well-established (49–52), and has been attributed to poorer HRQOL, sleep disorders, and reduced work productivity (49).

Peripheral sensory neuropathy.—Higher grades of peripheral sensory neuropathy were associated with a 2-fold greater use of medications for anxiety and/or depression. Our finding confirms previous reports in either TCS or other adult-onset cancer survivors of significant associations between peripheral neuropathy and anxiety (4,53–55) or depression (54–56). Since our study is cross-sectional, causal inferences cannot be made; moreover, the relation between peripheral neuropathy and anxiety/depression may be bidirectional. The

reciprocal adverse effects of pain and depression/anxiety on one another are well-established (57,58). The pain and reduced physical activity associated with peripheral neuropathy could increase anxiety/depression. On the other hand, patients with anxiety might experience and report a greater degree of neuropathy, perhaps due to shared biological pathways involved in the production of inflammatory cytokines in both anxiety and peripheral neuropathy (54). Similarly, patients with depression may experience more severe and persistent pain as the result of deficiencies in neurotransmitters (e.g., serotonin, norepinephrine) that may occur in depressed states (59). Thus, it has been suggested that antidepressants can decrease pain signals by increasing serotonin and norepinephrine levels in the brain (59).

Health insurance.—Having health insurance was associated with an increased use of medications for anxiety and/or depression, which likely reflects readier access to the health care system, including paid prescription medications (45).

Physical activity.—Our TCS engaged in vigorous physical activity were about 37% less likely to use medications for anxiety and/or depression. Physical activity can improve symptom management and HRQOL (physical, psychological, social, and spiritual) among cancer survivors (60). Moreover, physical activity is recommended in cancer survivorship guidelines published by the National Comprehensive Cancer Network, in part due to its effectiveness in reducing symptoms of both anxiety and depression (61).

Employment status.—Being employed was associated with a significantly lower use of medications for anxiety and/or depression. The association between unemployment and depression has been shown in the general population (62–64). We previously showed that peripheral sensory neuropathy (OR=2.44: grade 3 vs. 0, P=0.006), patient-reported HL (OR=1.82: grade 2/3 vs. 0, P=0.04), and pain (OR=3.75: grade 2/3 vs. 0, P<0.001) were associated with TCS unemployment (30). However, reasons for unemployment are mixed, since influences related to characteristics of both cancer survivors (e.g., sociodemographic and socioeconomic factors, and comorbidities) and employers (e.g., accommodation for cancer-related and treatment-related adverse effects) can influence employment status (65). Thus, multidisciplinary approaches, including physical, psychological, and vocational considerations, are required to understand employment and work outcomes among cancer survivors (65).

Strengths and Limitations

Strengths of this study include the large sample size and comprehensive assessment of sociodemographic features, health behaviors, and cisplatin-related AHOs using validated questionnaires. Medications used for anxiety and/or depression were defined according to pharmacological classes using published metrics (31,32), and stringent rules classified patients as users of these medications only if they specifically indicated that the reason for use was for one of these conditions. A rigorous approach was used to select independent variables and build multivariable models (45). Limitations include those inherent to all cross-sectional designs in that causal inferences cannot be made, since the temporal sequence of events cannot be ascertained. For example, it is not known whether unemployment preceded the use of medications for anxiety and/or depression or vice versa.

Additionally, patients with anxiety or depression may not have been prescribed these medications, may not have been compliant in taking these medications, or may not have reported medication use. Therefore, the number of patients taking medications for anxiety or depression could be less than the actual number of patients with these disorders. Moreover, information with regard to medication use for anxiety and or depression, employment status, and individual cisplatin-related AHOs (HL, tinnitus, peripheral neuropathy, and kidney disease) prior to chemotherapy was not available. Thus it is not known whether these factors were cancer/chemotherapy-related; however, given the young median age of our population, it is unlikely that AHO's were pre-existing (3).

Conclusion

In view of the significant associations we found between vigorous physical activity and less usage of medications for anxiety and/or depression, healthcare providers should encourage TCS to increase physical activity to improve both physical and mental health (66). In order to support employment and work resumption after cancer treatment, rehabilitation programs should incorporate tools that improve physical and psychological performance, assess work-related skills, and provide career development counseling/training and when possible, counseling for employers (65).

The association of higher grades of tinnitus and peripheral neuropathy with greater use of medications for anxiety and/or depression should prompt healthcare providers to actively address these conditions in TCS. Strategies such as acoustic stimulation, cognitive behavioral therapy, and educational counseling can alleviate tinnitus symptoms (67). Although no medications have been approved to treat tinnitus (18), antidepressants may have modest efficacy as an adjunct treatment to nonpharmacological treatments (52,68). To manage chemotherapy-induced peripheral neuropathy, guidelines support the use of duloxetine to treat associated pain, but there is limited scientific evidence for the use of other medications (69). Further research is required to prospectively investigate the efficacy of symptom management interventions for tinnitus and peripheral neuropathy in reducing anxiety and depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AHOs	Adverse health outcomes
CBCT	Cisplatin-based chemotherapy
CI	Confidence interval

CBM	Cumulative burden of morbidity
GCT	Germ cell tumor
HL	Hearing loss
MET	Metabolic equivalent task
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratios
Pt	Platinum
TCS	Testicular cancer survivors
VIF	Variance inflation factor

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Table 1.

Clinical and Sociodemographic Characteristics, and Health Behaviors of 1,802 Survivors of Cisplatin-Treated Germ-Cell Tumors (GCT) According to Prescription Medication Use for Anxiety and/or Depression

Clinical characteristic	Total No. (%)	Use of medications for anxiety and/or depression,[r] No. (%)	
	1,802	No (N= 1,651)	Yes (N= 151)
Age at GCT diagnosis, years			
Median (range)	30 (10–63)	30 (10–63)	31 (10–54)
<20	140 (7.8)	127 (7.7)	13 (8.6)
20–29	728 (40.4)	676 (40.9)	52 (34.4)
30–39	580 (32.2)	536 (32.5)	44 (29.1)
≥ 40	354 (19.6)	312 (18.9)	42 (27.8)
Age at clinical evaluation, years			
Median (range)	37 (18–75)	37 (18–75)	39 (18–64)
<30	428 (23.8)	397 (24.1)	31 (20.5)
30–39	644 (35.7)	598 (36.2)	46 (30.5)
40–49	429 (23.8)	388 (23.5)	41 (27.2)
50–59	240 (13.3)	214 (13.0)	26 (17.2)
≥ 60	61 (3.4)	54 (3.3)	7 (4.6)
Calendar year of diagnosis [a]			
Before 2000	195 (11.0)	183 (11.2)	12 (8.2)
2000–2009	609 (34.2)	552 (33.8)	57 (38.8)
2010–2017	976 (54.8)	898 (55.0)	78 (53.1)
Histologic type [b]			
Seminoma	438 (24.6)	403 (24.7)	35 (23.8)
Nonseminoma	1324 (74.4)	1214 (74.3)	110 (74.8)
GCT, not otherwise specified	18 (1.0)	16 (1.0)	2 (1.4)
Site of GCT [c]			
Testis	1588 (89.2)	1461 (89.5)	127 (86.4)
Extragonadal	192 (10.8)	172 (10.5)	20 (13.6)
Cisplatin-based chemotherapy [d]			
BEP [e]	1009 (56.3)	920 (56.1)	89 (58.4)
EP [f]	657 (36.7)	605 (36.9)	52 (34.4)
Other [g]	126 (7.0)	116 (7.1)	10 (6.6)
Cumulative dose of cisplatin, mg/m^2 [h]			
Median (range)	400 (100–1402.8)	400 (100–1400)	400 (100–800)
<300	123 (6.9)	110 (6.7)	13 (8.7)
300	643 (36.0)	596 (36.4)	47 (31.3)

Clinical characteristic	Total No. (%)	Use of medications for anxiety and/or depression,[r] No. (%)	
	1,802	No (N= 1,651)	Yes (N= 151)
301–399	79 (4.4)	72 (4.4)	7 (4.7)
400	838 (46.9)	769 (47.0)	69 (46.0)
>400	104 (5.8)	90 (5.5)	14 (9.3)
Time since completion of chemotherapy, years [i]			
Median (range)	3.8 (1–35.1)	3.8 (1–35.1)	3.8 (1–29.9)
<2	553 (31.8)	511 (32.1)	42 (28.8)
2-<5	464 (26.7)	422 (26.5)	42 (28.8)
5-<10	355 (20.4)	327 (20.5)	28 (19.2)
≥ 10	366 (21.1)	332 (20.9)	34 (23.3)
Sociodemographic characteristic			
Race [j]			
White	1484 (87.7)	1348 (87.2)	136 (93.2)
African American	18 (1.1)	16 (1.0)	2 (1.4)
Asian	77 (4.6)	73 (4.7)	4 (2.7)
Other	113 (6.7)	109 (7.1)	4 (2.7)
Education [k]			
High school or less	206 (11.9)	184 (11.7)	22 (14.7)
After high school but not college graduate	411 (23.8)	370 (23.5)	41 (27.3)
College or university graduate	726 (42.1)	677 (43.0)	49 (32.7)
Post-graduate	382 (22.1)	344 (21.8)	38 (25.3)
Employment status [l]			
Unemployed	114 (6.7)	94 (6.0)	20 (13.3)
Employed	1526 (89.0)	1411 (90.2)	115 (76.7)
Retired	34 (2.0)	31 (2.0)	3 (2.0)
On disability leave	40 (2.3)	28 (1.8)	12 (8.0)
Marital status [m]			
Single or never married	569 (33.2)	527 (33.6)	42 (29.0)
Married/living as married	1039 (60.6)	949 (60.5)	90 (62.1)
Divorced/separated	107 (6.2)	94 (6.0)	13 (9.0)
Health insurance coverage [n]			
No	156 (9.0)	148 (9.3)	8 (5.3)
Yes	1580 (91.0)	1438 (90.7)	142 (94.7)
Health behavior			
Smoking status [o]			
Never	995 (57.3)	922 (58.1)	73 (48.7)
Former	591 (34.0)	527 (33.2)	64 (42.7)

Clinical characteristic	Total No. (%)	Use of medications for anxiety and/or depression,[r] No. (%)	
	1,802	No (N= 1,651)	Yes (N= 151)
Current	150 (8.6)	137 (8.6)	13 (8.7)
Average no. alcoholic drinks in past year [p]			
Rarely or never	355 (20.5)	315 (19.9)	40 (26.5)
1–3 per month	235 (13.6)	208 (13.2)	27 (17.9)
1–6 per week	807 (46.6)	750 (47.4)	57 (37.8)
≥ 1 per day	336 (19.4)	309 (19.5)	27 (17.9)
Engage in vigorous physical activity (≥ 6 METs) [q]			
Yes	1180 (67.9)	1098 (69.1)	82 (55.0)
No	557 (32.1)	490 (30.9)	67 (45.0)

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; GCT, germ cell tumor; MET, metabolic equivalent of task; VeIP, vinblastine, ifosfamide, and cisplatin; VIP, etoposide, ifosfamide, and cisplatin.

[a] Calendar year of diagnosis was not available for 22 participants.

[b] Histologic type was not available for 22 participants.

[c] Germ cell tumor site was not available for 22 participants.

[d] Fifty-nine (3.3%), 723 (40.4%), 940 (52.5%), and 68 (3.8%) participants received ≤ two, three, four, and five or more cycles of cisplatin-based chemotherapy, respectively. Chemotherapy regimen and number of cycles was not available for 10 and 12 participants, respectively.

[e] Includes 252 (25.0%) participants with modification of dosing and schedules of BEP. The remaining 757 participants (75%) received the standard dosing and standard BEP schedule: each chemotherapy cycle consisted of bleomycin, 30,000 IU days 1, 8, and 15; etoposide 100 mg/m^2 days 1 through 5; and cisplatin 20 mg/m^2 days 1 through 5. Median cumulative cisplatin doses for the BEP group were 300 mg/m^2 (range, 100 to 900 mg/m^2).

[f] Includes 312 (47.5%) participants with modification of dosing and schedules of EP. The remaining 345 participants (52.5%) received the standard dosing and standard EP schedules: each chemotherapy cycle consisted of etoposide 100 mg/m^2 days 1 through 5 and cisplatin 20 mg/m^2 days 1 through 5. The median cumulative cisplatin doses for the EP group were 400 mg/m^2 (range, 110 to 1403 mg/m^2).

[g] Of 126 participants, 66 received VIP, 35 received cisplatin and ifosfamide; 9 received cisplatin, bleomycin, etoposide, and ifosfamide; two received VeIP. For the remaining 14, other combinations of cisplatin-based chemotherapy were applied.

[h] Cisplatin dose information was not available for 15 participants.

[i] Information on time since completion of chemotherapy was not available for 64 participants.

[j] Race was not stated for 110 participants.

[k] Educational status was not stated for 77 participants.

[l] Employment status was not stated for 88 participants.

[m] Marital status was not stated for 87 participants.

[n] Health insurance coverage was not stated for 66 participants.

[o] Smoking status was not stated for 66 participants.

[p] Average no. of alcoholic drinks in past year was not stated for 69 participants.

[q]Physical activity was assessed in this study based on a validated questionnaire (21–23). Participants were asked about the type of physical activity (walking; jogging (>10 min/mile); running ≤ 10 min/mile); bicycling; aerobic exercise; lower intensity excursive such as yoga, stretching, and toning; tennis, squash, or racquetball; lap swimming; weight lifting or stretch swimming) and average time per week (during the past year) spent at each of these activities. A MET score was assigned to each physical activity based on its energy cost. Vigorous physical activity was defined based on activities with MET value ≥ 6 (23). Physical activity information was not provided by 65 participants.

[r]Based on self-reported prescription medications taken for at least the past 4 weeks. Medication indication was classified as used for anxiety and/or depression according to both (1) its pharmacological class (31,32) and (2) if patients indicated its use was for anxiety and/or depression. Participants could report use of more than one medication for anxiety and/or depression. Medications used by 151 participants include alprazolam (n=15), amitriptyline (n=2), bupropion (n=10), buspirone (n=3), citalopram (n=15), clomipramine (n=2), clonazepam (n=24), desvenlafaxine (n=1), duloxetine (n=9), escitalopram (n=29), fluoxetine (n=11), fluvoxamine (n=1), imipramine (n=1), lorazepam (n=8), mirtazapine (n=1), nortriptyline (n=1), paroxetine (n=13), sertraline (n=20), trazodone (n=6), and venlafaxine (n=13).

Table 2.

Cisplatin-Related Cumulative Burden of Morbidity (CBM_{Pt}) Score and Patient-Reported Outcomes for 1,802 Survivors of Cisplatin-Treated Germ-Cell Tumors

	Total No. (%)	Use of medications for anxiety and/or depression, No. (%)	
Characteristic	**1,802**	**No (N= 1,651)**	**Yes (N= 151)**
CBM_{Pt} score [a]			
None	511 (28.4)	492 (29.8)	19 (12.6)
Very low	622 (34.5)	582 (35.3)	40 (26.5)
Low	334 (18.5)	292 (17.7)	42 (27.8)
Medium	287 (15.9)	244 (14.8)	43 (28.5)
High	48 (2.7)	41 (2.5)	7 (4.6)
Included in CBM_{Pt} score			
Patient reported hearing loss [b]			
None	1118 (62.0)	1052 (63.7)	66 (43.7)
Grade 1	427 (23.7)	379 (23.0)	48 (31.8)
Grade 2	235 (13.0)	200 (12.1)	35 (23.2)
Grade 3	22 (1.2)	20 (1.2)	2 (1.3)
Tinnitus [c]			
None	1091 (60.5)	1027 (62.2)	64 (42.4)
Grade 1	454 (25.2)	411 (24.9)	43 (28.5)
Grade 2	128 (7.1)	108 (6.5)	20 (13.3)
Grade 3	129 (7.2)	105 (6.4)	24 (15.9)
Peripheral sensory neuropathy [d]			
None	806 (44.7)	765 (46.3)	41 (27.2)
Grade 1	514 (28.5)	472 (28.6)	42 (27.8)
Grade 2	247 (13.7)	210 (12.7)	37 (24.5)
Grade 3	235 (13.0)	204 (12.4)	31 (20.5)
Patient-reported kidney disease [e]			
None	1760 (97.7)	1616 (97.9)	144 (95.4)
Grade 1	37 (2.1)	31 (1.9)	6 (4.0)
Grade 2	5 (0.3)	4 (0.2)	1 (0.7)

[a] CBM_{Pt} score calculated based on patient self-reported outcomes related to cisplatin (hearing loss, tinnitus, peripheral sensory neuropathy, and kidney disease) based on methods as described previously (15).

[b] Patient-reported hearing loss was graded using questions from Hearing Handicap Inventory by Ventry and Weinstein (27), Scale for Chemotherapy-Induced Long-Term Neurotoxicity (SCIN) questionnaire (25), and the European Organization for Research and Treatment of Cancer Chemotherapy Induced Peripheral Neuropathy 20-item quality-of-life questionnaire (EORTC-CIPN-20) (26).

[c] Tinnitus was graded with the Scale for Chemotherapy-Induced Long-Term Neurotoxicity (SCIN) questionnaire on the basis of symptoms experienced over the past 4 weeks (25).

[d] Peripheral sensory neuropathy was graded according to the EORTC-CIPN-20 questionnaire, the SCIN questionnaire, and patient-reported current prescription medication use. Prescription medications were only considered if the respondent stated that the indication was for neuropathy (15).

[f] Kidney disease was graded using patient-reported information on physician-diagnosed condition and current prescription medication use. Prescription medications were only considered if the respondent stated that the indication was for the adverse health outcome of interest (15).

Table 3.

Final Multivariable Models of the Association Between Various Factors and Use of Medications for Anxiety and/or Depression.

Variable	***Multivariable Model with Cisplatin-related Adverse Health Outcomes*** [d]		***Multivariable Model with CBM_{Pt}*** [e]	
	OR (95%CI)	***P* value**	**OR (95%CI)**	***P* value**
Vigorous physical activity (≥ 6 METs)				
No	Ref.		Ref.	
Yes	0.63 (0.44–0.89)	**0.01**	0.63 (0.44–0.90)	**0.01**
Employment status				
Unemployed	Ref.		Ref.	
Employed	0.39 (0.23–0.66)	**0.0005**	0.38 (0.23–0.65)	**0.0004**
Retired	0.35 (0.09–1.32)	0.12	0.33 (0.09–1.20)	0.09
On disability leave	1.19 (0.47–3.00)	0.71	1.21 (0.56–3.00)	0.68
Health insurance coverage				
No	Ref.		Ref.	
Yes	2.15 (1.01–4.56)	0.05	2.12 (1.00–4.82)	0.05
Tinnitus [a]			*Not included*	
None	Ref.			
Grade 1	1.46 (0.95–2.22)	0.08		
Grade 2	2.20 (1.25–3.88)	**0.007**		
Grade 3	2.74 (1.89–4.75)	**0.0003**		
Peripheral sensory neuropathy [b]			*Not included*	
None	Ref.			
Grade 1	1.30 (0.82–2.06)	0.26		
Grade 2	2.20 (1.33–3.63)	**0.002**		
Grade 3	1.68 (0.99–2.87)	0.06		
CBM_{Pt} score [c]	*Not included*			
None			Ref.	
Very low			1.46 (0.83–2.57)	0.19
Low			2.96 (1.67–5.24)	**0.0002**
Medium			3.47 (1.95–6.18)	**<0.0001**
High			3.18 (1.22–8.30)	**0.02**

Abbreviations: AHOs, adverse health outcomes; CBM_{Pt}, cumulative burden of morbidity score (related to cisplatin); confidence interval; OR, odds ratio; Ref., reference.

Note: *P* values with boldface indicate significance at $P < 0.05$.

[a]Tinnitus was graded with the Scale for Chemotherapy-Induced Long-Term Neurotoxicity (SCIN) questionnaire on the basis of symptoms experienced over the past 4 weeks (25).

[b] Peripheral sensory neuropathy was graded according to the EORTC-CIPN-20 questionnaire, the SCIN questionnaire, and patient-reported current prescription medication use. Prescription medications were only considered if the respondent stated that the indication was for neuropathy (15).

[c] CBM_{Pt} score was calculated based on the number and severity of AHOs following methods adapted from Geenen et al(29) as described previously (15). The CBMpt score encompasses cisplatin-related AHOs of HL, tinnitus, peripheral sensory neuropathy, and kidney since each has been previously shown to be related to CBCT (1,2,20).

[d] The odds ratios and *P* values are from an adjusted binomial logistic regression model that includes employment status, engagement in vigorous physical activity, tinnitus, peripheral sensory neuropathy, and health insurance coverage as independent variables with the use of medications for anxiety and/or depression (yes/no) as the outcome (dependent) variable. Variables with omnibus (Wald chi-square from type 3 analysis of effects) $P > 0.1$ were removed from the final model in a backward deletion procedure. The omnibus *P* value for the variables listed in the table include: employment status ($P = 0.0004$), engagement in vigorous physical activity ($P = 0.01$), tinnitus ($P = 0.0009$), peripheral sensory neuropathy ($P = 0.02$), and health insurance coverage ($P = 0.05$).

[e] The odds ratios and *P* values are from an adjusted binomial logistic regression model that includes employment status, engagement in vigorous physical activity, and CBM_{Pt} with use of medications for anxiety and/or depression (yes/no) as the outcome (dependent) variable. Variables with omnibus $P > 0.1$ were removed from the final model in a backward deletion procedure. The omnibus *P* value for the variables listed in the table include: employment status ($P = 0.0002$), engagement in vigorous physical activity ($P = 0.01$), CBM_{Pt} ($P < 0.0001$), and health insurance coverage ($P = 0.05$).

[f] Tumor stage was not associated with the use of medications for anxiety/depression in the univariate model ($P=0.34$) or in multivariable models adjusted for either adverse health outcomes ($P=0.23$) or CBM_{Pt} score ($P=0.24$)